Author’s response to reviews

Title: Non specific pattern of lung function in a respiratory physiology unit: causes and prevalence: results of an observational cross-sectional and longitudinal study

Authors:

Brigitte Chevalier-Bidaud (brigitte.chevalier-bidaud@hmn.apphp.fr)
Karine Gillet-Juvin (karine.juvin@egp.apphp.fr)
Etienne Callens (etienne.callens@wanadoo.fr)
Romain Chenu (romain.chenu@egp.apphp.fr)
Sémia Graba (dr.graba@neuf.fr)
Mohamed Essalhi (mohamed.essalhi@egp.apphp.fr)
Christophe Delclaux (christophe.delclaux@egp.apphp.fr)

Version: 3
Date: 13 June 2014

Author’s response to reviews:

We thank the two Reviewers for their helpful comments, which helped us to improve our manuscript.

Response to the first reviewer (Paul Scanlon)

Major comments

Comment 1) In the original description by Hyatt et al, it was noted that although obstructive disorders constitute a majority of cases of the nonspecific pattern, a minority consist of non-obstructive disorders. These include obesity, muscle weakness, other forms of chest wall limitation, and heart failure. I would suggest you address some composite of these in defining the frequency of disorders, lest your readers think this can only be caused by obstruction. Further, I would point out in your discussion that chest wall limitation, whether due to weakness, obesity, pleural disease, or other anatomic limitation (e.g. scoliosis) can cause the nonspecific pattern in the clear absence of airway obstruction.

Response. The Reviewer raises an important issue. From a physiological point of view, a reduction in FEV1 can only be related to either obstructive or restrictive or mixed defects. Normal TLC eliminates the two latter defects, and thus the pattern would be obstructive. Hyatt and colleagues clearly stated that they “find it difficult to present a unifying mechanism to explain the NSP (nonspecific pattern) in group B” (no obvious airway involvement). Overall, they further stated in their conclusion that “thirty-two percent of subjects had no evidence of airway disease”, which does not mean that these patients had no airway obstruction based on a functional point of view. Interestingly, they emphasized that “the conditions and mechanism described for group B (nonairway) are suggestive of restriction despite the low normal TLC.” One may hypothesize that these latter patients with beginning restrictive defect have collapse of small airways. This
collapse may be favoured by some degree of airway responsiveness that is increased in obese patients (50% in the study of Hyatt and colleagues). Along this line, we recently demonstrated that the prevalence of airway hyperresponsiveness is increased in obese women (see ref 16).

It has to be stated that the ATS/ERS Task force classified this pattern as obstructive: “special attention must be paid when FEV1 and FVC are concomitantly decreased and the FEV1/FVC ratio is normal or almost normal. This pattern most frequently reflects failure of the patient to inhale or exhale completely. It may also occur when the flow is so slow that the subject cannot exhale long enough to empty the lungs to RV. In this circumstance, the flow–volume curve should appear concave toward the end of the manoeuvre. TLC will be normal and FEF75 will be low. Measurement of slow VC (inspiratory or expiratory) may then give a more correct estimate of the FEV1/VC ratio. Another possible cause of this pattern is patchy collapse of small airways early in exhalation [8, 49–52]. Under these conditions, TLC may be normal, but RV is ordinarily increased.”

We now have modified the discussion section as: “These authors emphasized that some patients had no evidence of airway disease. Restricted expansion of the thorax or lung may have explained the NSP in most of these subjects since the conditions were suggestive of restriction despite the low normal TLC. Interestingly, some of these conditions have also been associated with increased airway responsiveness [17, 18], which may have favoured the occurrence of this NSP”. Two additional references have been quoted.

Comment 2) Results, Paragraph 2 - it is not sufficiently clear from your description how you narrowed the 360 patients with key diagnoses down to 185, or if that is a valid selection process. Please describe and justify further.

Response. In the Figure 1 legend we stated that: “The first step allowed the selection of patients instead of LFT (from 841 LFT to 360 patients): 30 patients with miscellaneous diseases (see Methods) were excluded, and 360 patients were selected (451 tests were follow-up LFT). All these 360 patients had the “NSP” diagnosis selected by the physician in charge of the medical report, based on the results of LFT showing the predicted value of each parameter and their 5th percentile (95th percentile for absolute lung volumes, additionally) based on normative equations for spirometry and lung volumes with correction for ethnicity [12, 13]. Consequently, the prevalence of NSP in each lung disease was calculated from this sample. The next step was conducted to describe lung function test results from a highly selected subgroup with indisputable diagnoses. For the purpose of the study a more recent Caucasian set of predicted values for spirometry was used [11] allowing the calculation of Z-scores.”

We now have modified this legend (second step of the selection design): “The next step was conducted to describe lung function test results from a highly selected subgroup with indisputable diagnoses. For the purpose of the study a more recent Caucasian set of predicted values for spirometry was used [11] allowing the calculation of Z-scores. After the exclusion of non Caucasian subjects and patients with a smoking history # 15 pack-year for non
COPD/emphysema diagnoses, 185 / 360 patients were available for the final description”.

Comment 3) Obesity seems to be less prevalent in your patients than in Hyatt's. However, there is no attempt to describe the prevalence of obesity among your 12,775 cohort, nor the 841 with NSP, nor the selected groups of 360 or 185, however they were selected. Differences between Europe and North America are important in this regard, and may be the main reason for the slightly lower prevalence of the NSP among your patients. Please address this major issue.

Response. The number of patients obese, being overweight and with normal weight have now been added in Table 1, according to the comment. We agree that the lower prevalence of obesity may contribute to the lower prevalence of NSP in our population that is now discussed as: “We similarly observed that asthmatic patients in our series were often obese, even if obesity prevalence was lower in our series (26%), which may further explain our lower prevalence of NSP”.

Comment 4) Discussion, paragraph 7: Is it true that patients were only included in your analysis if interpreting physicians identified them as such at the time of interpretation? That seem open to a large number of patients being misidentified as obstruction or restriction, particularly with the vagaries of different interpreting physicians. This could totally bias your estimate of the prevalence of the NSP to an inappropriately low value.

Response. It is true. The ATS/ERS task force guidelines were available on December 2005. In 2006, we already implemented these recommendations in our LFT Unit. Since 2007, an interface has been implemented in our computerized chart allowing the interpretation of LFT according to recommendations. Given the low number of physicians writing the medical reports (Karine Gillet-Juvin, Etienne Callens, Sémia Graba, Mohamed Essalhi and Christophe Delclaux) and their involvement in clinical research, we do think that the estimate of our prevalence is not totally biased. Nevertheless, we acknowledge that this prevalence may have been underestimated to some extent, which has already been stated in the discussion section as: “Data extraction was based on the actual recording of NSP by the physician in charge of the LFT report made in the routine practice; consequently, the observed prevalences could have been underestimated”.

Comment 5) Conclusion: Although plethysmographic lung volumes can be enlightening, I believe it is an overstatement that plethysmographic lung volumes, an expensive test, is mandatory when FVC and FEV1 are reduced. While the availability of accurate lung volumes may prevent the incorrect impression of a restrictive disorder in those who turn out to have the NSP, the need for such information varies depending on previous measurements, lung imaging, and clinical judgment. If resources or time are limited, measurement of maximal respiratory pressures may sometimes be considerably more valuable.

Response. We agree that plethysmographic lung volume measurement is
required depending on previous measurements, lung imaging, and clinical judgment, which is now clearly stated in the revised version of our manuscript as: “Thus, the measurement of static lung volumes by body plethysmography can be helpful in presence of FEV1 and FVC reduction, depending on previous measurements, lung imaging, and clinical judgment.”

Minor comments

Materials and Methods:
Comment 1) Please provide reference for "RECORD" or explain.
Response. The link has now been added in the manuscript (new extension of STROBE).

Comment 2) Design, Paragraph 1, end - you describe what has recently been called a "complex restrictive pattern" (Dykstra et al, at both World Chest Congress and ATS, 2014). It is not the same as a mixed obstructive/restrictive disorder which is described in the 2005 ATS/ERS Interpretive Standard and requires a reduced FEV1/FVC ratio.
Response. We agree with the comment of the Reviewer, and we have modified the sentence accordingly.

Comment 3) Design, second to last paragraph - have you measured the inter-device variation in measurements between your two systems? How does that affect repeat measures? Viasys is now part of CareFusion.
Response. According to recommendations, daily calibrations are used, and biological (healthy subjects) calibrations are also used periodically on the different devices to ensure that similar results are obtained from our different devices. We think that it does not significantly affect repeat measures. CareFusion has now been added.

Comment 4) Statistics: I would include the methods detailed in Table 2.
Response. This has been made, accordingly.

Comment 5) Results, Paragraph 2: among English speakers, the term “hyperinflation” is usually applied to instances of significant increase in TLC, whereas increased RV or FRC is usually called "air trapping”. Neither term is defined in the ATS/ERS interpretive Standards paper, so older references must be used. It should be noted, first, that increased RV is virtually universal in the non-specific pattern (see Table 1 in Hyatt). It should also be noted, as above, that this may be due to either airflow obstruction or, less commonly, due to chest wall limitation.
Response. The term hyperinflation has been replaced by air trapping accordingly to the comment. The new discussion also states that: “In the presence of a normal TLC, a decrease in VC, and therefore of FEV1, is the consequence of an increase in RV. Pathologic conditions associated with intrinsic and extrinsic
obstruction of small airways, together with expiratory muscle weakness, will lead to an increased RV."

Comment 6) Discussion, end of Para 5: Do you ever measure airway resistance in patients with NSP? Our technicians routinely identify patients with NSP and, following a clinical laboratory protocol, and measure Raw when the NSP is identified. In non-published data, we find that only about half of patient with NSP have increased Raw.

Response. In our lab, the measurement of airway resistance is systematically made when volumes are measured using body plethysmography. The table 1 shows that Rawtot is 154 ± 99% predicted in the 185 patients, and if an upper normal limit of 150% is chosen (as done in clinical practice), ~50% of our patients demonstrate an increase in airway resistance, accordingly with the Reviewer comment.

We already stated in the discussion section: “The mild to moderate lung air trapping that was evidenced in our study together with an increase in airway resistance further suggest distal airway obstruction. Along this line we showed that both airway resistance and specific airway resistance can augment in the presence of peripheral airway obstruction [24, 25].”

Discretionary:
Intro, para 1, line 13 - "... the other depicted..." could be better stated as "...the others suffered from...."
Results, Para 2: "Asthmatics depicted..." could be better stated "Asthmatics demonstrated..."
Follow-up, paragraph 1, line 4: How long was the mean interval of follow-up?
Substitute "demonstrated" for "depicted".

Response. All the suggested modifications have now been made.

Response to the second reviewer (Jesper Magnusson)

Reviewer's report:
This is in general, an excellent article. I have but one major comment.

Comment 1. Major Revision. The authors choose to include bilateral lung transplanted (BLT) patients in their material and generalize their discussion to the entirety of their material. New lungs give the patient a new normal. The sizefit of the donors lung into to the recipient cannot be assumed to be perfect thus applying percentiles from a normal material to this population is precarious. FEV1 and concomitantly FVC reduction is observed rather frequently among lung transplant recipients but macroscopic conditions like diminished bronchial diameter due to proliferation in the anastomoses as well as bronchiomalacia are all too common. Since the special properties of BLT patients is not commented upon, the discussion and the conclusion can be partially called into question.
Response. We agree with the Reviewer that the special properties of BLT patients would have been commented upon. We now have added in the discussion section the following paragraph: “Interestingly, in patients with bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation, Bergeron and colleagues identified two functional phenotypes: a typical obstructive lung defect and an atypical obstructive lung defect with a concomitant decrease in the FEV1 and FVC with a normal total lung capacity (31% of the patients, 95% CI: 21 to 42%). Consequently, this latter prevalence is similar to ours, and one may hypothesize that this high prevalence is specifically related to obliterative bronchiolitis [17] rather than to biases related to the presence of lung size mismatching between donor and recipient, and/or inaccurate predicted values for donor lungs”. Two new references have been quoted.